American Journal of Pathology, Vol. 162, No. 6, June 2003

This Month in *AJP*

Roles of Vascular Endothelial Growth Factor (VEGF) and Fibroblast Growth Factor-2 (FGF-2) in Tumor Angiogenesis

Dr. Harold Dvorak, the recipient of the 2002 Rous-Whipple Award from the American Society for Investigative Pathology presents a review based on the award lecture (Am J Pathol 2003, 162:1747–1757). The article discusses the multiple effects of vascular endothelial growth factor (VEGF) on vessel permeability, angiogenesis, stroma formation, and lymphangiogenesis. It also provides a historical account of its discovery.

Among the angiogenic factors produced by tumors, VEGF and FGF-2 are of particular importance and may play a major role in sustaining tumor growth. However it is not know whether these growth factors interact in their angiogenic activities. Recent data suggest that that inhibition of FGF-2 in tumor grafts blocks angiogenesis, even in the presence of high VEGF levels. Giavazzi et al (Am J Pathol 2003, 162:1913–1926) established lines of human endometrial adenocarcinoma cells in which expression of FGF-2 was inducibly regulated while VEGF activity could be blocked with an anti-sense cDNA. Simultaneous expression of FGF-2 and VEGF in cells transplanted into nude mice produced fast-growing tumors with high blood vessel density. Blockade in either FGF-2 or VEGF resulted in a decrease in vessel density and tumor burden. However inhibition of VEGF but not of FGF-2 caused tumor hypoxia and necrosis. Thus, VEGF and FGF-2 may act synergistically to enhance tumor angiogenesis, but appear to have different targets in the process of blood vessel formation.

Telomerase Gene Amplification in Embryonal Tumors of the Central Nervous System

Embryonal central nervous system (CNS) tumors are the most frequent brain tumors of childhood. The *hTERT* gene, encoding the telomerase catalytic subunit, is generally not expressed in normal somatic cells but may be active in tumors. This gene and the mRNA coding for the hTERT protein have not been analyzed in detail in embryonal tumors, although gain of material in the 5p15 chromosomal region at which the *hTERT* is located, has been reported. Fan et al (Am J Pathol 2003, 162:1763–1769) determined the *hTERT* copy number and hTERT mRNA expression in CNS embryonal tumors, using differential and real-time polymerase chain reaction techniques. They report that the *hTERT* gene was amplified in 15 of 36 tumors examined and that the level of amplification was highly correlated with hTERT mRNA expression. It is possible that increased hTERT expression may correlate with more aggressive tumor growth and invasion in medulloblastomas. In any case, the data show that the hTERT gene may be involved in the pathogenesis of CNS embryonal tumors.

High Levels of Lymph Vessel Formation in Metastatic Melanoma

Malignant melanomas metastasize both by the blood and lymphatic routes. Although some reports suggest that blood microvessel density may correlate with metastatic potential, the issue remains controversial. Melanomas spread early through lymphatics to reach regional lymph nodes, and involvement of sentinel nodes is used for staging of melanomas. Nevertheless, it is not known with certainty if melanomas induce lymphangiogenesis and whether this process may be related to metastatic spread. Dadras et al (Am J Pathol 2003, 162:1951–1960) report that tumor lymphangiogenesis does occur in human primary malignant melanomas and that the density of the lymph vessels is higher in metastatic tumors. No differences were observed in the density of tumor-associated blood microvessels or VEGF expression. Although this important issue requires further study, the data indicate that that the extent of tumor lymph vessel formation may correlate with the metastatic potential of malignant melanomas.

Reciprocal Relationship Between Expression of Collagen and Metalloproteinase Genes in Liver Stellate Cells

Stellate cells produce collagen and extracellular matrix components in liver fibrosis. However, the development of hepatic fibrosis depends not only on fibrogenesis by stellate cells but also of the activity of metalloproteinases that degrade collagens and tissue inhibitors of proteinases. Schaefer et al (Am J Pathol 2003, 162:1771–1780) tested the hypothesis that there is a reciprocal regulation of genes coding for collagen I and metalloproteinase 13 (MMP-13) in stellate cell lines. Clones that expressed high levels of collagen mRNA did not express MMP-13 and MMP-2. Conversely, stellate cell clones that are low collagen mRNA expressors, express high levels of MMPS, which are also inducible by

tumor necrosis factor. These results contribute to our understanding of the regulation of hepatic fibrosis by demonstrating that collagen formation and extracellular matrix degrading enzymes are reciprocally regulated in stellate cells.

Growth and Differentiation of Gastric Surface Cells in Culture

Gastric epithelial cell progenitors are located in the isthmus and generate all epithelial lineages of the stomach that migrate up or down from the isthmus. The pit cell lineage migrates from the isthmus into the luminal surface and differentiates into surface mucous cells. It has been suggested that pit cell differentiation is highly dependent of interactions between these cells and the surrounding stroma. Ootani et al (Am J Pathol 2003, 162:1905–1912) developed a co-culture method to reconstruct gastric mucosal surface in a tri-dimensional collagen gel system. Gastric epithelial cells placed in culture showed immature features. However, when co-cultured with fibroblasts, the cells differentiated into mature surface mucous-containing, columnar-shaped cells. Cell differentiation and apoptosis was modulated by modifications of the air-liquid interface of the cultures. This co-culture system is an excellent model for the study of the pathobiology of gastric epithelium.